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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/692,807	10/20/2000	Ghazwan Saleem Butrous	PC10370A	6255

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/692,807	BUTROUS ET AL.	
	Examiner	Art Unit	
	Dwayne C. Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03NOV2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-10 and 21-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-10 and 21-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/3/04; 5/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 8-10 and 21-112 are pending.

2. Claims 8-10 and 21-112 are rejected.

3. Claims 1 and 7 are cancelled as per the amendment of November 4, 2004.

4. Claims 2-6 and 11-20 were previously cancelled.

Response to Arguments

5. Applicants' arguments November 4, 2004 have been fully considered but they are not persuasive with respect to the prior art teaching Ellis et al. Applicants argue the following issues. First, applicants allege that applicants allege that Ellis et al. do not disclose the use of sildenafil for the treatment of pulmonary hypertension. Second, applicants state that applicants claims are not "obvious to try" in view of Ellis et al.

6. First, applicants allege that Ellis et al. do not disclose the use of sildenafil for the treatment of pulmonary hypertension. Ellis et al. specifically teach that inhibitors of cGMP-PDE clearly teach of treating hypertension and pulmonary hypertension, (see page 2). In fact, Ellis et al. refer to EP 463,756, which in turn teaches of pyrazaolopyrimidinone compounds, which clearly render the instant invention obvious. The skilled artisan would have been motivated to use sildenafil and other PDE inhibitors to treat pulmonary hypertension. Due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension, it would have been inherent that this particular compound of sildenafil is also a PDE V inhibitor. The fact that applicants

have further specified a particular isozyme of this enzyme, in this case the type V isozyme of PDE, is an inherent trait or property with the administration of the compounds of Ellis et al. as well as EP 463,756. Accordingly, it would have been obvious to the skilled artisan to use the very same PDE inhibitory compounds, such as sildenafil, to treat pulmonary hypertension. In addition, the skilled artisan is clearly provided with the motivation to use any type V phosphodiesterase inhibitor for the vascular smooth muscle relaxation (vasodilation) in mammals with pulmonary hypertension due to the fact that the very same compound, namely sildenafil, is shown to treat pulmonary hypertension, it would have been inherent that this particular compound of sildenafil is also a PDE V inhibitor.

7. Second, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Due to the explicit teaching of Ellis et al. the skilled artisan is provided with motivation to use PDE V inhibitors to treat pulmonary hypertension, (see page 2, 2nd full paragraph). Clearly, this provides the skilled artisan with motivation to use an inhibitor of PDE V to treat pulmonary hypertension as well as giving the artisan with an expectation of success of treating the ailment of pulmonary hypertension with

8. Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). This selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The skilled artisan would have been motivated to treat patients with an inhibitor of PDE V to treat pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). In fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs).

Information Disclosure Statement

9. The information disclosure statements filed on November 3, 2004 and May 2, 2005 have been reviewed and considered, see enclosed copies of PTO FORMs 1449.

Claim Rejections - 35 USC § 103

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. The rejection of claims 8-10 and 21-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ellis et al. of WO 94/28902 possessing a publication date of December 22, 1994, especially for sildenafil and its derivatives is maintained and repeated for both the above-stated and reasons of record. Ellis et al. teach of compounds that are potent inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs). This selective enzyme inhibition lead to elevated cGMP levels which, in turn, provides the basis for many utilities, namely the treatment of hypertension and pulmonary hypertension, (see page 2, 2nd full paragraph). The skilled artisan would have been motivated to treat patients with pulmonary hypertension irrespective of its cause, such as respiratory distress, neonatal hypoxia, post operatively, chronic hypoxia, COPD because Ellis et al. clearly disclose to the artisan

that these inhibitors of cGMP PDE are used to treat both hypertension and pulmonary hypertension. Ellis et al. specifically teach of inhibitors of cGMP PDEs with the compounds of formula (I). In fact, Ellis et al. disclose of "[a] particularly preferred group of compounds of formula (I)" is obtained when R^1 is methyl; R^2 is n-propyl; R^3 is ethyl; R^4 is $SO_2NR^9R^{10}$; R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4-N(R^{12})-piperazinyl group; and R^{12} is methyl, (see page 6, 2nd full paragraph). Ellis et al. also teach of pharmaceutically acceptable salts of the compounds of formula (I), (see page 5, 1st and 2nd full paragraphs). Ellis et al. teach of various modes of administration for these compounds, inter alia, oral and parenteral administration, (see page 10). Ellis et al. further teach of a dosing administration in man ranging from 5 to 75 mg of the compound three times daily, (see page 10, 4th full paragraph). The determination of a dosage having the optimum therapeutic index, modes and methods of administration, for instance inhalation, as well as age of the patient is well within the level of one having ordinary skill in the art, and the artisan would be motivated to determine optimum amounts to get the maximum effect of the drug. Accordingly, the Ellis et al. reference renders the instantly claimed invention obvious.

Obviousness-type Double Patenting

13. The rejection of claims 8-10, and 21-112 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 8 of U.S. Patent No. 5,250,534 is withdrawn in response to the remarks of November 4, 2004.

14. The rejection of claims 8-10, and 21-112 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,2, and 4 of U.S. Patent No. 5,346,901 is withdrawn in response to the remarks of November 4, 2004.

15. The rejection of claims 8-10, and 21-112 are directed to an invention not patentably distinct from claims 8-4 of commonly assigned of U.S. Patent No. 5,250,534 is withdrawn in response to the remarks of November 4, 2004.

16. The rejection of claims 8-10, and 21-112 are directed to an invention not patentably distinct from claims 1,2, and 4 of commonly assigned of U.S. Patent No. 5,346,901 is withdrawn in response to the remarks of November 4, 2004.

Conclusion

17. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Wednesdays, and Fridays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, may be reached at (571) 272-0951. The official fax No. for correspondence is (571)-273-8300.

Also, please note that U.S. patents and U.S. patent application publications are no longer supplied with Office actions. Accordingly, the cited U.S. patents and patent application publications are available for download via the Office's PAIR, see http://pair-direct.uspto.gov. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free).

DWAYNE JONES
PRIMARY EXAMINER
Tech. Ctr. 1614
June 8, 2005